REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 47-54 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claim 51 has been objected to because of informalities. Appropriate correction is now made to claim 51, thereby obviating this objection.

Claims 47-50 and new claims 51-54 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for the recitation of "comprises constant regions" because the examiner finds unclear as to what it is the "constant regions" of. Claims 47-50 have been amended to make clear the "constant regions", thereby obviating this rejection.

Claims 47-50 remain rejected, and new claims 51-54 are rejected are under 35 U.S.C. 103(a) as being unpatentable over Taniguchi et al. (*J. Immunol. Methods*, 1997, 206:107-113), in view of Kohno et al. (*Clin. Immnopath.*, January 1998, 86(1):11-15), and Reichmann et al. (*Nature*, 1988, 332-323-327). The examiner states that, even though none of the references teaches an artificially produced peptide capable of neutralizing IL-18, and its use in treatment, the suggestion or motivation to do so can be found based on combination of references, which teach a

mouse anti-human IL-18 monoclonal antibody capable of neutralizing IL-18 (by Taniguchi), a pathological role of IL-18 in diseases such as RA and methods of administering anti-IL-18 antibodies for treating a pathological condition (by Kohno), and a method of making a humanized antibody minimizing the anti-globulin response during therapy (by Riechmann). The examiner concludes that it is logical and obvious to one of skill in the art to antagonize the action of IL-18 in treating RA by using an artificially produced peptide capable of neutralizing IL-18, such as a humanized antibody. This rejection is respectfully traversed.

Taniguchi discloses an IL-18 monoclonal antibody, which neutralizes IL-18. Taniguchi discloses that patients suffering from RA show higher level of IL-18 (see page 113, left column, third paragraph). It should be noted, however, that Taniguchi never teaches that Taniguchi IL-18 monoclonal antibody is effective to treat RA. Taniguchi, in fact, does not disclose the peptide of the presently claimed invention at all. Taniguchi, furthermore, suggests nothing about whether the peptide of the claimed invention is effective in treating the specified diseases including RA.

Kohno never confirms if IL-18 antibody is actually effective to treat the diseases such as diabetes and RA. Kohno, like Taniguchi, does not disclose the peptide of the presently

claimed invention at all. Kohno suggests nothing about whether the peptide of the presently claimed invention is effective to treat the specified diseases including RA.

Even though the examiner indicates that Riechmann discloses a method of making a humanized antibody minimizing the anti-globulin response during therapy, it should be noted that Riechmann does not disclose a general technique for making humanized antibody that is applicable to every kind of antibodies, but discloses an "antibody against CAMPATH-1 antigen" only. Furthermore, Reichmann states at page 325, left column, lines 5-6, that:

> There are mAbs to many cell-type specific differenciation antigens, *but only a few* have therapeutic potential. (emphasis added)

Riechmann thus teaches that only a few antibodies among those specific to antigens is effective in terms of therapy. In other words, Riechmann *per se* teaches that, even if humanized antibodies of the anti-IL-18 antibodies disclosed in Taniguchi or Kohno are obtained in accordance with the teachings of Riechmann, it is unclear whether the obtained humanized anti-IL-18 antibodies are actually effective to treat RA until the experiment is carried out.

In view of the above, applicants believe that the examiner has used hindsight to reconstruct applicants' presently claimed invention. The Federal Circuit Court of Appeals stated

in *In re Gorman* 18 USPQ2d 1885, 1888 (Fed. Cir. 1991); citing *Interconnect Planning Corp. v. Feil* 227 USPQ 543, 551 (Fed. Cir. 1985), that:

> It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using applicant's structure as a template and selecting elements from references to fill the gaps... The references themselves must provide some teaching whereby the applicant's combination would have been obvious.

Without hindsight, the presently claimed invention is not made obvious by the cited and applied references.

Applicants believe that certainty is required for an invention relating to a method for treating a living body. Accordingly, applicants believe that the presently claimed invention should not be rejected over the cited and applied references which provide no certainty with regard to the effectiveness of humanized IL-18 antibody in treating RA.

Riechmann further discloses at page 325, right column, last paragraph to page 326, left column, second paragraph, that the rat CAMPATH-1 antibody, when humanized, shows drastically decreased binding activity to CAMPATH-1. This clearly shows that making a humanized antibody may result in losing inherent functions of the antibody so that the humanized antibody is not capable of being used to neutralize an antigen. In this regard, applicants believe that it would not have been obvious even to

those of skill in the art whether or not making a humanized antibody of a specific antibody is indeed advantageous.

Accordingly, even if one of skill in the art may have been motivated by the disclosures of Taniguchi, Kohno and Riechmann to obtain humanized IL-18 antibody, it would not have been obvious whether the resulting humanized IL-18 antibody is actually effective for treating RA without undue experimentation. None of the cited references applied by the examiner discloses the peptide of the presently claimed invention. None of the cited references either alone or in combination provides reliable information about the effectiveness of the claimed humanized antibody in treating RA.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above amendments and comments, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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